REMARKS

The Office Action of July 31, 2003 presents the examination of claims 1-5, 18, 19, 31 and 32. Claims 6-13, 17 and 20-30 stand withdrawn from consideration in view of restriction of the claims.

Rejoinder requested

The agreement of the Examiner to later consider rejoinder of method of use claims limited in scope to allowed composition claims at the proper time is noted. Rejoinder has until the present time been held in abeyance. Applicants believe that the instant claims represent allowable subject matter. The Examiner is also reminded of Applicants' prior argument that claims directed to pharmaceutical compositions comprising a recited nucleic acid have been improperly restricted from claims to the nucleic acid per se. The Examiner is requested to rejoin appropriate subject matter from withdrawn claims 6-13, 17 and 20-30 to the instant application.

IDS

The Examiner still has not returned a form PTO 1449 indicating acknowledgment of filing of the Ferrara reference, first listed on a form PTO-1449 filed with the Information Disclosure Statement of June 20, 2001. A copy of that reference and another copy of the form PTO-1449 were sent with Applicants' response of May 30, 2003. The Examiner is respectfully requested to send an initialed PTO form 1449 acknowledging consideration of the Ferrara reference with the next communication.

Formal Matters

Claims 2 and 3 stand objected to as improperly dependent upon claim 1. The Examiner indicates that claims 2 and 3 are improperly broader than claim 1 from which they depend. Claims 2 and 3 are canceled, rendering this objection moot.

Rejection under 35 USC § 112, first paragraph

Claims 2, 3, 31 and 32 stand rejected under 35 USC § 112, first paragraph, as allegedly unsupported by enabling disclosure in the specification. Claims 2, 3, 31 and 32 are canceled, rendering this rejection moot.

Rejection over prior art

Claims 1-5, 18, 19, 31 and 32 stand rejected under 35 USC § 102(e) as anticipated by Schreiner et al., U.S. Patent 6,351,975. Claims 2, 3, 31 and 32 are canceled, rendering the rejection moot as to these claims. This rejection is respectfully traversed as to the remaining claims 1-5, 18 and 19.

The claims of the present application are directed to the 114 amino acid variant of VEGF. On the other hand, Schreiner '975 discloses the 121 amino acid variant of VEGF. Thus, the molecule disclosed by Schreiner '975 is distinct from the present invention.

The Examiner takes a position that these structurally distinct molecules are expected to have the same biological activities. Applicants assert the contrary position.

The distinct molecules of the invention and disclosed by Schreiner '975 arise in a cell due to alternative splicing of a transcript of a VEGF gene. Because there have evolved cellular mechanisms for producing these splice variants, the ordinarily-skilled artisan would suppose that

these two forms of VEGF would have different biological activities. This supposition is supported by the evidence provided in the three abstracts provided herewith in Exhibit B.

J.M. Cherng et al. (2000) explain that angiogenesis is regulated by five isoforms of VEGF, of 121, 145, 165, 189 and 206 amino acids, respectively. Cherng et al. point out that, "different VEGF isoformes amy mediate distinct endothelial cell functions." Cherng et al. (1997) compare three variants of VEGF (121, 165 and 189). The results presented indicate that VEGF121 and VEGF165 have similar physiological activities, but VEGF189 has a different physiological activity, lacking a hemorrhage- causing activity. Houck et al. (1991) explain that there is unpredictability in the biological activities of the various splice variants. VEGF121 and VEGF165 were both observed to exhibit endothelial cell mitogenic activity, but this activity was not seen for VEGF189 or VEGF206. Also, VEGF121 and VEGF165 were observed to encode signal peptides and be secreted, while VEGF189 and VEGF206 remained cell-associated. Houck et al. conclude that different patterns of secretion suggest different physiological roles for the different isoforms.

Data provided in the attached Declaration of Dr. Zoya Gluzman-Poltorak and Kelly Boren further support an expectation that VEGF114 has different biological activities from VEFG121. These data show that VEGF114 has less potent effects on endothelial cell proliferation and apoptosis than VEGF165, and unlike VEGF165, has no effect on sprouting in a three-dimensional *in vitro* angiogenesis assay. The Examiner might note that, in an *in vivo* assay for angiogenic activity, VEGF121 showed a slightly *higher* activity than VEGF165. (See the Cherng (2000) abstract in Exhibit B.)

The VEGF114 of the present invention is structurally distinct from the VEGF121 of Schreiner '975. The preponderance of the evidence of record establishes that one of ordinary skill in the art would expect that the VEGF114 of the present invention has a different activity compared to

VEGF121 of Schreiner '975. At least this evidence establishes that the biological activity of one isoform of VEGF is not predictable from the activities exhibited by another isoform. Accordingly, the instant invention is not anticipated by Schreiner '975 and the instant rejection should be withdrawn. Neither is there any basis for the Examiner to assert that the instant invention is obvious in view of Schreiner '975 and such a rejection should not be made as a new ground of rejection.

Applicants submit that the present application well-describes and claims patentable subject matter. The favorable action of withdrawal of the standing rejections and objections and issuance of the claims is respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17; particularly, extension of time fees.

Respectfully submitted,

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Attachments: Exhibit B
Unexecuted Declaration under 37 CFR § 1.132 (Executed Declaration to follow)